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(54) Title: SURGICAL IMPLANT COATED WITH A COMPOSITION COMPRISING A POLYOL FATTY ACID MONOESTER

(57) Abstract: A surgical implant has a basic structure with an at least partial coating. The implant comprises alpha-hydroxycarboxylic acid oligomers (preferably lactic acid oligomers) and/or provides these ase decomposition product after implantation. The coating includes polyol fatty acid monoester, preferably glycerol fatty acid monester. The implant has an antimicrobial action.

SURGICAL IMPLANT COATED WITH A COMPOSITION COMPRISING A POLYOL FATTY ACID MONOESTER

The invention relates to surgical implants (including surgical suturing threads) having antimicrobial properties.

There are many possible ways of providing surgical implants and medical products with bactericidal or antimicrobial properties, in particular coatings with the active substance triclosan, or triclosan as a constituent of a resorbable coating, and further the addition of silver (see, for example, US 2001/0010016 A1: medical products with triclosan and silver compound; US 2001/0055622 A1: antimicrobial bioabsorbable materials, silver in a bioabsorbable substrate), the addition of antibiotics, of bactericidal substances of plant origin or of other substances such as quaternary ammonium compounds or cyanoacrylates, iodine and iodine-containing compounds. Examples of antimicrobial active substances are to be found, for instance, in K.H. Wallhäuser: Praxis der Sterilisation Desinfektion Konservierung [Practice of sterilization disinfection preservation], 5th edition, 1995.

In DE 195 21 642 A1, an implant is described which consists of resorbable material on surface areas protected against infection and which contains an antimicrobial active substance. In this case, the solubility of the antimicrobial active substance is chosen so that it is released substantially throughout the entire period of degradation of the material.

US 4 024 871 discloses surgical suture material in which a multifilament strand is impregnated with an antimicrobial agent and is coated on the surface with a segmented polyurethane polymer. This coated suture material retains its antmicrobial action over an extended period of time.

Surgical suture material with a long-lasting antimicrobial action is also known from US 3 987 797. The suture material contains an elastomeric ionically bonded block copolymer of polyquaternary polyurethane.

A disadvantage is that often the active substances are not positionally stable on the implants, for example because they dissolve too readily in body fluids; the action *in situ* on the implant is then too short because the effective dose is available only for a short time. Conversely, however, an antimicrobial action over too long a period of time can also be undesirable.

A further disadvantage is that the implants in many cases cannot be sterilized by conventional methods, for example ethylene oxide gas, because the process conditions necessary for this (temperature, pressure and time) lead to changes in the concentration of the active substance (sublimation, evaporation, etc.; for example in the case of triclosan or lactic acid) or the active substances react or lose their efficacy, for example, through oxidation with ethylene oxide (for example antibiotics which are sensitive to oxidation). The use of gamma rays (cobalt sterilization) can lead to difficulties because chlorine-containing substances, for example triclosan or chlorhexidine, cannot easily be sterilized by radiation (formation of chlorine-containing aromatic reaction products).

Some active substances have a sensitizing action and cannot therefore be considered for use or implantation in humans. Silver does not break down in the body.

WO 00/71789 A1 discloses hydrophilic polypropylene fibres with antimicrobial activity which are suitable for absorbent layers and wound dressings. Glycerol monolaurate is added to the polypropylene in the melt, optionally with a further additive for enhancing the hydrophilicity. The antimicrobial properties of the glycerol monolaurate are im-

proved if lactic acid is applied to the surface of the fibres, this lactic acid being sprayed on in aqueous solution during production.

US 5,208,257 and EP 0 530 861 A2 describe topical antimicrobial pharmaceutical compositions which contain glycerol fatty acid ester (in particular glycerol monolaurate), a mixture of fatty acids, and a carrier. Lactic acid can be added as chelating agent to the carrier.

The document JP 20024852 A discloses an antimicrobial nonwoven textile structure in which polylactide fibres are used.

US 4 002 775 discloses the preservation of foodstuffs with 1- or 2-glycerol monolaurate.

The object of the invention is to develop an effective and biocompatible way of providing surgical implants with antimicrobial properties, without having to greatly modify existing production and sterilization techniques.

This object is achieved by a surgical implant having the features of Claim 1 and by methods of manufacturing such an implant in accordance with Claims 13 to 18. Advantageous embodiments of the invention are set out in the dependent claims.

The surgical implant according to the invention has a basic structure and an at least partial coating. The coating includes polyol fatty acid monoester. The implant also comprises alpha-hydroxycarboxylic acid oligomers and/or provides alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation.

By means of the active substance combination of polyol fatty acid monoesters (preferably glycerol fatty acid monoester) and alpha-hydroxycarboxylic acid oligomers

(preferably dimers of lactic acid or oligomers of lactic acid with more than two units), a temporary antimicrobial action is obtained for the implant. These active substances are biocompatible and can be broken down in the body. The decomposition products are inert and/or are excreted, they are physiologically safe and, after implantation, they act for a defined period of time which can be set.

The duration of the antimicrobial action can be controlled via the degree of decomposition of the oligomeric lactic acid in the implant. Monomeric lactic acid or oligomers of lactic acid are antibacterial and strengthen the antibacterial action of the glycerol fatty acid monoesters, so that, as a result of the decomposition of the oligomeric lactic acid, a sufficiently high level of lactic acid and of low-molecular-weight oligolactic acid is obtained over the period of resorption.

The implant according to the invention can already contain the alpha-hydroxycarboxylic acid oligomers when supplied. However, as an alternative, or in addition to this, alpha-hydroxycarboxylic acid oligomers can also develop, after implantation, as decomposition product from implant substance. Thus, resorbable polymers of polyhydroxy acids (e.g. a copolymer of glycolide and lactide in a ratio of 90:10 sold by Ethicon under the name "Vicryl") form oligomeric hydroxy acids during resorption, for example oligolactic acid. Low-molecular-weight oligomers are to be expected to be present at fairly high concentrations only after a considerable degree of decomposition (for example, in the case of Vicryl, only after more than 30 days, or, in the case of the predegraded "Vicryl" material sold by Ethicon under the name "Vicryl Rapid", only after more than ca. 5 days). If so desired, however, the implant or suture material according to the invention can already be provided with alpha-hydroxycarboxylic acid oligomers when supplied, so that, after just a short time of implantation

(for example after a few hours, or later, for example up to 3 weeks after implantation) it provides and releases a sufficiently high concentration of oligomeric hydroxy acids.

A further advantage is that products with the implant according to the invention can be produced, in a form which is stable during storage, by means of customary sterilization methods (for example gas sterilization with ethylene oxide or sterilization with cobalt gamma rays). Problems of the kind which are to be expected in the case of impregnation with monomers of lactic acid, namely an initially strong and unwanted reaction of the body tissue or a possible change in concentration upon ethylene oxide sterilization as a result of evaporation of the lactic acid under the prevailing pressure and temperature conditions, do not arise.

The coating preferably comprises a resorbable matrix. In this way, it is possible to control the timing of the release of the polyol fatty acid monoester and if appropriate of the alpha-hydroxycarboxylic acid oligomers (if these are included in the coating). A resorbable matrix can for example be made up of polymers and copolymers which are soluble in organic solvents (for example polylactides or polycaprolactones, or, for example, compounds composed of polytetramethylene adipates or the like).

The coating can also be non-resorbable. If a coating with a non-resorbable matrix is present, the matrix is preferably porous so that the polyol fatty acid monoester or monoesters and if appropriate the alpha-hydroxycarboxylic acid oligomers included in the coating have access to the surrounding body tissue or tissue fluids so as to be able to deploy their antimicrobial action. With the aid of the resorbable or non-resorbable matrix, the readily water-soluble decomposition products (in particular lactic acid

or low-molecular-weight oligolactic acid) can temporarily bind to the implant in a stable position. Non-resorbable coatings can be produced, for example, on the basis of silicones or polyvinyl acetates. The access to the antimicrobial active substances can also take place through swelling of the coating, by which means the coating takes up tissue fluids, which thus come into contact with polyol fatty acid monoester or alpha-hydroxycarboxylic acid oligomers.

As has already been indicated, the coating can include alpha-hydroxycarboxylic acid oligomers and/or can provide alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation. Alternatively, or in addition to this, it is conceivable for the basic structure to provide alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation.

Examples of preferred alpha-hydroxycarboxylic acid oligomers are dimers of L-lactic acid, higher oligomers of L-lactic acid, dimers of D-lactic acid, higher oligomers of D-lactic acid, dimers of DL-lactic acid, higher oligomers of DL-lactic acid, oligomeric copolymers of glycolide and lactides, and mixtures of the abovementioned substances. "Higher" oligomers are to be understood here as oligomers with more than two structural units.

The production of oligomeric lactic acid is described, for example, in the document GB 2 135 320 A, the disclosure of which is taken up in the present application. Oligomeric lactic acid is also obtainable as a commercial product. The inherent viscosity, which is a measure of the degree of polymerization, serves for characterization. Thus, for example, Alkermes supplies what are called "Medisorb Polymers" with inherent viscosities in the range of 0.08 dl/g to 0.80 dl/g (type 5050 DL 1A with an inherent viscosity of 0.08 dl/g to 0.012 dl/g, and type 5050 Dl 4A with an inherent viscosity of 0.38 dl/g to 0.48 dl/g). Polyscience

supplies poly(DL-lactic acid) with an inherent viscosity of 0.15 dl/g to 0.30 dl/g and with an inherent viscosity of 0.35 to 0.45 dl/g and poly(L-lactic acid) of different degrees of polymerization and also poly(DL-lactide/glycolide) and poly(L-lactide/glycolide) of different degrees of polymerization. The inherent viscosity preferably lies in the range of 0.01 dl/g to 0.8 dl/g. Oligomeric copolymers of, for example, glycolide and lactides are also described in GB 2 135 320 A; here the molar mass is indicated instead of the inherent viscosity, because the inherent viscosity cannot be measured in standard solvents.

As hydroxycarboxylic acid derivatives or lactic acid derivatives, it is also possible, for example, to use so-called "monomer residues" from the processing or production of resorbable polymers.

Examples of polyol fatty acid monoesters are 1-glycerol fatty acid monoester having a fatty acid residue of a saturated fatty acid with 6 to 18 carbon atoms, preferably with 6, with 12 or with 18 carbon atoms, 2-glycerol fatty acid monoester having a fatty acid residue of a saturated fatty acid with 6 to 18 carbon atoms, preferably with 6, with 12 or with 18 carbon atoms, 1-glycerol fatty acid monoester with a fatty acid residue of an unsaturated fatty acid, 2-glycerol fatty acid monoester with a fatty acid residue of an unsaturated fatty acid, and mixtures of the abovementioned substances.

The coating can, for example, comprise copolymers of glycolide and lactides, preferably of 35 wt-% glycolide and 65 wt-% L-lactide, predegraded copolymers of glycolide and lactides, copolymers of caprolactone and glycolide, copolymers of caprolactone and lactides, copolymers of caprolactone, glycolide and lactides, polytetramethylene adipate, copolymers of aliphatic diols and aliphatic di-

carboxylic acids, or soluble polyurethanes but also, for example, silicones or polyvinyl acetates.

Resorbable coatings of L-lactides/glycolides in different mixing ratios are particularly preferred. Such coatings can at the same time be a source of alpha-hydroxycarboxylic acid oligomers (lactic acid derivatives/hydroxycarboxylic acid derivatives) which are released during resorption and have an antimicrobial action (see above). The molar mass of the coating is preferably chosen such that a wax-like covering is obtained.

Resorbable coatings with polytetramethylene adipate are particularly suitable for polyester (e.g. for polyethylene terephthalate PET), for example in the case of non-resorbable suture material made of PET, like the suture material sold by Ethicon under the name "Ethibond". Copolymers of caprolactone and glycolide/lactides are known as suture material coatings.

The surgical implant according to the invention can be configured for numerous different applications. Generally, the nature of the application is determined by the form of the basic structure. Examples of implants and their basic forms are: suturing threads, surgical sutures, cord-like implants, tape-like implants, areal implants, films, mesh-like implants, mesh-like implants with small pores, mesh-like implants with large pores, three-dimensional implants (i.e. implants with a relatively large extent in all three spatial directions), textile structures of every kind, voluminous fleece-like implants, implants for dura replacement, suture-bearing implants, constructs for tissue formation, constructs for cell colonizing, tubes, wires, stents, drainages, catheters, vessel prostheses.

The basic structure can be resorbable, non-resorbable or partially resorbable. Examples of materials of or in the basic structure are: biocompatible metals, steel, tita-

nium, nitinol, metal alloys, ceramics, glasses, silicones, natural polymers, synthetic polymers, resorbable polymers, polypropylene, polyvinylidene fluoride, fluorinated polyolefins, polyesters, polyethylene terephthalate, polymers and copolymers of lactides, glycolides, caprolactone and/or trimethylene carbonate, predegraded copolymers of glycolide and L-lactide, poly-p-dioxanone, polyurethanes.

In the case of predegraded material, a resorbable material undergoes preliminary treatment leading to more rapid resorption after implantation. In particular, copolymers of glycolide and L-lactide can be predegraded by treating them in a hydrolysis buffer or by irradiation. An example of such a material is "Vicryl Rapid" (see above). It is also conceivable to predegrade the resorbable portion of a finished basic structure (e.g. in partially resorbable implants or suture material). As has already been mentioned above, this permits more rapid provision of alpha-hydroxycarboxylic acid oligomers.

In advantageous embodiments of the invention, the coating includes (in addition to polyol fatty acid monoesters and if appropriate alpha-hydroxycarboxylic acid oligomers) at least one biologically active substance, for example natural ingredients, synthetic ingredients, antibiotics, chemotherapeutics, cytostatics, metastasis inhibitors, antidiabetics, antimycotics, gynaecological agents, urological agents, anti-allergic agents, analgetics, neuroleptics, antirheumatics, anti-inflammatory agents, antimicrobial agents, sexual hormones, sexual hormone inhibitors, haemostyptics, hormones, peptide hormones, antidepressants, antihistamines, naked DNA, plasmid DNA, cationic DNA complexes, RNA, cell constituents, vaccines, cells occurring naturally in the body, genetically modified cells. In addition to the stated antimicrobial properties (which can also have an antiproliferative character, as is shown in Example 9 below), the implant can be given further fea-

tures, for example extended antimicrobial and/or antiproliferative properties.

In preferred embodments, the coating amounts to 0.1% to 20% of the total weight of the implant.

There are many possible methods of manufacturing an implant according to the invention. In a preferred embodiment, the coating is applied to the basic structure as a solution or dispersion. The solution or dispersion contains a matrix material, alpha-hydroxycarboxylic acid oligomers, polyol fatty acid monoester and a solvent or dispersing agent. The solvent or dispersing agent is subsequently evaporated. The solution or dispersion preferably includes 1 wt-% to 30 wt-% of matrix material (for example the basic materials mentioned above for the coating), 0.1 wt-% to 10 wt-% of alpha-hydroxycarboxylic acid oligomers, 0.1 wt-% to 10 wt-% of polyol fatty acid monoester, optionally up to 30 wt-% of additional substances, and solvent or dispersing agent, preferably an organic solvent or dispersing agent, as balance.

If the solution or dispersion includes copolymers of glycolide and lactides or predegraded copolymers of glycolide and lactides as matrix material (and in addition to these also polyol fatty acid monoester and a solvent or dispersing agent), addition of alpha-hydroxycarboxylic acid oligomers can be dispensed with, even if the basic structure contains no alpha-hydroxycarboxylic acid oligomers or does not provide them as decomposition product.

To create a two-stage coating, a solution or dispersion with alpha-hydroxycarboxylic acid oligomers and polyol fatty acid monoester in a solvent or dispersing agent (without matrix material or binder or only with a slight addition thereof) is first applied to the basic structure. After evaporation of the solvent or dispersing agent, a further layer is applied.

Dipping or spraying methods, for example, are suitable for applying the solution or dispersion.

The implant can finally be sterilized with ethylene oxide. This is because the antimicrobial active substances are not impaired, or are not impaired to any appreciable extent, as explained above, under the conditions which then prevail. Sterilization with gamma rays, for example cobalt radiation, is likewise possible.

The invention is explained in more detail below on the basis of examples.

Example 1

Surgical suture material of "Vicryl" (Ethicon; copolymer of glycolide and lactide in a ratio of 90:10) can be provided with an antimicrobial coating in analogy to standard methods for thread coating of suture material.

A suitable coating mixture for "Vicryl" threads (thread strengths according to USP of between 9-0 and 6) is a mixture with a coating copolymer of glycolide/L-lactide as matrix material (4.5 wt-% to 7.5 wt-%), calcium stearate (manufactured by Malinckrodt Chemical Inc; 4.5 wt-% to 7.5 wt-%), L-oligolactic acid (Polyscience) (0.1 wt-% to 5 wt-%), glycerol monostearate (Albimono 90 V manufactured by AB Technologies Ltd; content of monoglycerides more than 90%, according to USP 23; 0.1 wt-% to 5 wt-%) and ethyl acetate as solvent and dispersing agent (remaining wt-%).

The coating is carried out in a one-stage method with subsequent "pliabilization". To do this, a bath with the above mixture is first set up. An uncoated thread is guided via rollers through this bath and subsequently

dried in a channel at ca. 50°C to 55°C. The coil material is then dried in vacuo for 16 hours at ca. 50°C. A "pliabilization" is then carried out; i.e. the wax-like coating is broken open by reeling it between pairs of rollers in order to enlarge the active surface and improve the handling of the thread; the thread is thus made softer. The thread contains ca. 0.5 to 20 weight percent (wt-%) of the coating components. The thread is finally finished, packed and sterilized.

In a concrete example, a "Vicryl" thread of strength 1 was passed through a bath made up as follows:

5 wt-% of G/L copolymer (35 wt-% of glycolide, 65 wt-% of lactide, inherent viscosity 0.4 dl/g to 0.8 dl/g),

5 wt-% of calcium stearate,

1 wt-% of oligolactic acid (poly(L-lactic acid), Polyscience; inherent viscosity 0.10 dl/g to 0.20 dl/g; molecular weight 1600 to 2400),

1 wt-% of glycerol monostearate,

dispersed in ethyl acetate (remaining wt-%).

The coating was carried out in the way described above; thereafter, the thread was packed and sterilized. The thread contained ca. 2 wt-% of the coating components.

The antimicrobial activity of the described sterile thread was determined using AATCC Test Method 100-1999 ("Assessment of antibacterial finishes on textile materials"), specifically with Staphylococcus aureus. Compared to an uncoated thread, there was a marked reduction of colony-forming units after an incubation period of 24 hours.

Example 2

In a coating according to example 1, glycerol monolaurate was used instead of glycerol monostearate. A plant-based glycerol monolaurate with the trade name "Monomuls", type 90-L-12 was used (produced by Grünau Illertissen; sold by Cognis Deutschland GmbH, Care Chemicals). This product is molecularly distilled and has a monoester content of at least 90%; the starting materials are coconut oil and glycerol.

Example 3

In a two-stage method, a mixture with oligolactic acid and glycerol fatty acid derivative in ethyl acetate or another suitable solvent or dispersing agent is first applied to the basic structure. After drying, a further coating with, for example, copolymers of lactide and glycolide or copolymers of glycolide and caprolactones is applied in a second stage. For this further coating, it is also possible to use a standard coating, as is employed for example in suture material.

Example 4

Threads of polyester (polyethylene terephthalate PET; sold by Ethicon under the name "Mersilene" or, coated, as "Ethibond") can be coated as in example 1. The coating bath contains glycerol monostearate, oligolactic acid, 3 wt-% to 15 wt-% of polytetramethylene adipate (produced by Ethicon; molar mass ca. 1100 to 3200 g/mol) as matrix material and, for example, toluene as solvent. The amount of solid applied to the thread is then ca. 0.5 wt-% to 15 wt-%. Thread strengths of between # 7-0 to strength 7 (USP) are suitable, but also, for example, cords with a diameter of 1 mm or more.

Example 5

In order to investigate the antimicrobial activity, a coating bath was first set up in accordance with the concrete recipe in example 1 (but without calcium stearate), and using glycerol monolaurate instead of glycerol monostearate. A sample of a section of "Vypro II" mesh (composite mesh of "Vicryl" and polypropylene yarns; Ethicon) was coated by dipping it into this coating bath and then drying it.

This mesh sample, provided with a coating containing glycerol monolaurate and an oligomeric lactic acid in a coating copolymer, was dipped for 5 seconds into a solution of Staphylococcus aureus with 10,000 CFU/ml (CFU: colony-forming units). The number of microbes on the mesh was determined immediately and after 1 hour, after 6 hours and after 24 hours (surface-sampling with Rodac plates).

For comparison purposes, an uncoated mesh was subjected to the same treatment.

Compared to the uncoated mesh, there was a marked reduction in the number of microbes after just 6 hours.

The test was repeated with Escherichia coli. Again, compared to an uncoated mesh, there was a marked reduction in the number of microbes after just one hour.

Example 6

In the manner already explained, and also described in example 5, areal implants and three-dimensional implants (for example fleeces) can likewise be made bactericidal or antimicrobial with alpha-hydroxycarboxylic acid oligomers

and polyol fatty acid monoester. Examples of basic structures which may be mentioned here are:

meshes made of "Vicryl" (copolymer of glycolide and lactide in the ratio of 90:10, Ethicon),

mesh pouches made of "Vicryl" (Ethicon),

"Vypro" meshes (composite meshes made of "Vicryl" and polypropylene, Ethicon),

"Mersilene" meshes (meshes made of polyester, Ethicon),

"Vypro II" meshes (composite meshes made of "Vicryl" and polypropylene yarns; Ethicon),

"Monocryl"-containing meshes (Ethicon; "Monocryl": copolymer of glycolide and epsilon-caprolactone),

other non-resorbable meshes, for example of "Pronova", a mixture of polyvinylidene fluoride and a copolymer of vinylidene fluoride and hexafluoropropene (Ethicon), or other composite meshes made up of resorbable and non-resorbable proportions, or tapes, e.g. a woven tape of polyester yarns (such as that sold by Ethicon under the name "Mersilene tape"),

cords, for example of polyesters or of resorbable materials,

fleeces, for example of "Vicryl" and poly-p-dioxanone yarns (trade name "Ethisorb" from Ethicon), but also, for example, needlefelts of "Vicryl" yarns,

drainages or catheters,

vessel prostheses,

implants of stainless steel, for example stents.

The coating can be applied to the basic structure in one stage, for example analogously to examples 1 and 4, or in two stages (e.g. analogously to example 3). Moreover, the coating can additionally be provided with further active substances.

A dipping method for applying the coating takes place for example analogously to example 1 (dipping, drying, packing and sterilization with ethylene oxide). Instead of using a dipping bath, a solution/dispersion of the coating agents can also be sprayed onto the basic structure.

In a further embodiment, the basic structure is dipped into a bath with a solution/dispersion of the coating agents and is then removed from the bath. The temperature is then increased so that the coating melts and penetrates into the basic structure. After drying and packing, sterilization is carried out with ethylene oxide.

Example 7

In the case of a "Vypro" mesh (Ethicon, see example 6), the "Vicryl" proportion can be predegraded by hydrolysis (e.g. at pH 7.26 in a phosphate buffer solution at ca. 50°C for two days, followed by brief washing and drying), so that an addition of oligolactic acid is not required since this is already provided by the hydrolysis. This is followed by impregnation with glycerol fatty acid monoesters and, optionally, additional coating.

An analogous method can be carried out with "Vicryl" meshes or with meshes containing "Monocryl" (see example 6). In the latter case, the hydrolysis is done, for example, for 5 days at 41°C in a phosphate buffer, with oli-

gomeric structural units arising from the glycolide proportion.

Example 8

Non-resorbable coatings can be produced for example on the basis of silicones.

Thus, for example, metal implants or medical products, as are described in DE 197 22 880 C1 for surgical needles, can be coated with different silicone oils in a plurality of stages, and the coating solutions can contain the antimicrobial active substances or also additional active substances. This method is also suitable, for example, for coating catheters made of silicones.

Other non-resorbable coatings can, for example, contain a matrix of polyvinyl acetates. Examples of suitable coating methods are dipping or spraying methods in which a solution of polyvinyl acetates and active substances in a suitable solvent is used.

Example 9

The therapeutic efficacy of a medical-quality stainless steel probe coated with a mixture containing oligolactic acid and glycerol monostearate was demonstrated in the following way:

1) LS174T cells (tumour cells) were cultured in a standard Petri dish (DMEM medium with 10% foetal bovine serum; 37° Celsius; 5% carbon dioxide). This preparation served as a control for a coated and an uncoated stainless steel probe.

2) A stainless steel probe measuring 3 cm in length was dipped several times into a 1:1 mixture of oligolactide and glycerol monostearate (Albimono 90 produced by AB Technologies Ltd) in THF (ca. 5% strength) and was dried with evaporation of the solvent THF. The coating had a thickness, viewable by microscope, of less than 50 micrometres. The probe was fixed on the bottom of a Petri dish by means of a magnet mounted on the outside of the Petri dish. The cultured LS174T cells were then transferred to this Petri dish.

3) Analogously to 2), an uncoated stainless steel probe was introduced into a Petri dish and fixed therein by a magnet. The cultured LS174T cells were then also transferred to this Peri dish. This preparation served as a control for the behaviour of a stainless steel probe not provided with a coating.

The status of the cells in preparations 1) to 3) was checked after 24 hours, 48 hours and 72 hours. The criterion used for evaluating the status of the cell cultures was the formation of a homogeneous cell lawn on the bottom of the culture dishes.

The findings were as follows: In the preparation described under 1), the cells multiplied normally and formed an almost homogeneous cell lawn. In the preparation described under 2), the status of the cell culture was markedly poorer after 24 hours. No almost homogeneous cell lawn had formed. After 48 hours and 72 hours too, no cells had grown on. In the preparation described under 3), the status of the cell culture was as in the control described under 1).

This investigation shows clearly that the coating of the stainless steel probe prevents the growth of the cells.

Claims

1. Surgical implant, having a basic structure and an at least partial coating, the implant comprising alpha-hydroxycarboxylic acid oligomers and/or providing alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation, and the coating including polyol fatty acid monoester.

2. Implant according to Claim 1, characterized in that the coating comprises a resorbable matrix.

3. Implant according to Claim 1, characterized in that the coating is non-resorbable or comprises a non-resorbable matrix.

4. Implant according to one of Claims 1 to 3, characterized in that the coating includes alpha-hydroxycarboxylic acid oligomers and/or provides alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation.

5. Implant according to one of Claims 1 to 4, characterized in that the basic structure provides alpha-hydroxycarboxylic acid oligomers as decomposition product after implantation.

6. Implant according to one of Claims 1 to 5, characterized in that the alpha-hydroxycarboxylic acid oligomers comprise at least one of the substances selected from the following group: dimers of L-lactic acid, higher oligomers of L-lactic acid, dimers of D-lactic acid, higher oligomers of D-lactic acid, dimers of DL-lactic acid, higher oligomers of DL-lactic acid, oligomeric copolymers of glycolide and lactides, mixtures of the above-mentioned substances.

7. Implant according to one of Claims 1 to 6, characterized in that the polyol fatty acid monoester comprises at least one of the substances selected from the following group: 1-glycerol fatty acid monoester having a fatty acid residue of a saturated fatty acid with 6 to 18 carbon atoms, preferably with 6, with 12 or with 18 carbon atoms, 2-glycerol fatty acid monoester having a fatty acid residue of a saturated fatty acid with 6 to 18 carbon atoms, preferably with 6, with 12 or with 18 carbon atoms, 1-glycerol fatty acid monoester with a fatty acid residue of an unsaturated fatty acid, 2-glycerol fatty acid monoester with a fatty acid residue of an unsaturated fatty acid, mixtures of the abovementioned substances.

8. Implant according to one of Claims 1 to 7, characterized in that the coating comprises at least one of the substances selected from the following group: copolymers of glycolide and lactides, preferably of 35 wt-% glycolide and 65 wt-% L-lactide, predegraded copolymers of glycolide and lactides, copolymers of caprolactone and glycolide, copolymers of caprolactone and lactides, copolymers of caprolactone, glycolide and lactides, polytetramethylene adipate, copolymers of aliphatic diols and aliphatic dicarboxylic acids, soluble polyurethanes, silicones, polyvinyl acetates.

9. Implant according to one of Claims 1 to 8, characterized in that the basic structure has one of the forms selected from the following group: suturing threads, surgical sutures, cord-like implants, tape-like implants, areal implants, films, mesh-like implants, mesh-like implants with small pores, mesh-like implants with large pores, three-dimensional implants, textile structures, voluminous fleece-like implants, implants for dura replacement, suture bearing implants, constructs for tis-

sue formation, constructs for cell colonizing, tubes, wires, stents, drainages, catheters, vessel prostheses.

10. Implant according to one of Claims 1 to 9, characterized in that the basic structure comprises at least one of the substances selected from the following group: biocompatible metals, steel, titanium, nitinol, metal alloys, ceramics, glasses, silicones, natural polymers, synthetic polymers, resorbable polymers, polypropylene, polyvinylidene fluoride, fluorinated polyolefins, polyesters, polyethylene terephthalate, polymers and copolymers of lactides, glycolides, caprolactone and/or trimethylene carbonate, predegraded copolymers of glycolide and L-lactide, poly-p-dioxanone, polyurethanes.

11. Implant according to one of Claims 1 to 10, characterized in that the coating includes at least one biologically active agent, which preferably comprises at least one of the substances selected from the following group: natural ingredients, synthetic ingredients, antibiotics, chemotherapeutics, cytostatics, metastasis inhibitors, antidiabetics, antimycotics, gynaecological agents, urological agents, anti-allergic agents, analgetics, neuroleptics, antirheumatics, anti-inflammatory agents, antimicrobial agents, sexual hormones, sexual hormone inhibitors, haemostyptics, hormones, peptide hormones, antidepressants, antihistamines, naked DNA, plasmid DNA, cationic DNA complexes, RNA, cell constituents, vaccines, cells occurring naturally in the body, genetically modified cells.

12. Implant according to one of Claims 1 to 11, characterized in that the coating amounts to 0.1% to 20% of the total weight of the implant.

13. Method of manufacturing an implant according to one of Claims 1 to 12, characterized in that the coating is applied to the basic structure as solution or dispersion,

the solution or dispersion containing a matrix material, alpha-hydroxycarboxylic acid oligomers, polyol fatty acid monoester and a solvent or dispersing agent, and in that the solvent or dispersing agent is subsequently evaporated.

14. Method according to Claim 13, characterized in that the solution or dispersion includes 1 wt-% to 30 wt-% of matrix material, preferably at least one of the substances according to Claim 8, 0.1 wt-% to 10 wt-% of alpha-hydroxycarboxylic acid oligomers, 0.1 wt-% to 10 wt-% of polyol fatty acid monoester, optionally up to 30 wt-% of additional substances, and solvent or dispersing agent, preferably an organic solvent or dispersing agent, as balance.

15. Method of manufacturing an implant according to one of Claims 1 to 12, characterized in that the coating is applied to the basic structure as solution or dispersion, the solution or dispersion including copolymers of glycolide and lactides or predegraded copolymers of glycolide and lactides as matrix material, polyol fatty acid monoester and a solvent or dispersing agent, and in that the solvent or dispersing agent is evaporated afterwards.

16. Method of manufacturing an implant according to one of Claims 1 to 12, characterized in that a solution or dispersion with alpha-hydroxycarboxylic acid oligomers and polyol fatty acid monoester in a solvent or dispersing agent is applied to the basic structure and in that, after evaporation of the solvent or dispersing agent, a further layer is applied.

17. Method according to one of Claims 12 to 16, characterized in that, finally, the implant is sterilized with ethylene oxide.

18. Method according to one of Claims 12 to 16, characterized in that, finally, the implant is sterilized with gamma rays, preferably cobalt radiation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12760

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L17/12 A61L17/14 A61L27/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 71183 A (3M INNOVATIVE PROPERTIES CO) 30 November 2000 (2000-11-30) page 1, line 1 -page 5, line 17 ---	1-18
Y	WO 00 71789 A (3M INNOVATIVE PROPERTIES CO) 30 November 2000 (2000-11-30) cited in the application page 2, line 20 - line 32 page 5, line 7 - line 27 page 9, line 25 -page 10, line 21 ---	1-18
Y	US 4 201 216 A (MATTEI FRANK V) 6 May 1980 (1980-05-06) *entire document* -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2004	27/02/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/12760

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